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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,184	02/12/2001	Howard Sands	12636-898	6040

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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,184	SANDS ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.0.0

DETAILED ACTION

The Request for Continued Examination and Amendments/Remarks are acknowledged. Claims 1-4 and 6-36 are included in the prosecution of this application. Claim 5 stands cancelled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "a phospholipid that does not tend to form micelle structures" does not have support in the specification as originally filed since recited microdroplets can be construed as micelles. If applicant asserts there is support for such an amendment, the examiner requests that the applicant provide the specific line and page of said support.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is directed to the composition comprising "up to about 25%" which is vague and indefinite since the term "up to" includes the value zero. The value cannot be zero since the independent claim requires camptothecin.

Claim 17 is directed to the composition comprising "up to about 5%" which is vague and indefinite since the term "up to" includes the value zero. The value cannot be zero since the independent claim requires camptothecin.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4, 8, and 12-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haynes (4725442) by itself or in view of Burke (5552156).

Haynes states microdroplets are known and consist of spheres of organic liquid phase drug approximately 500 Angstroms in diameter and range from 200 Angstroms up to at least one micron (10,000 Angstroms) in diameter and are covered with a monolayer of a suitable phospholipid. Haynes teaches microdroplets (200 angstroms up to a micron) of water insoluble drugs containing a pharmaceutically acceptable liquid surrounded by a layer of phospholipid, which are suitable for injection (Note the abstract, columns 2-8, and claims).

Although Haynes discloses his invention using anesthetics in examples, according to Haynes the microdroplets of the invention can be used to deliver **any water-insoluble/oil-soluble drug compound** via injection. See col. 1, lines 26-39. Moreover, Haynes teaches anti-

cancer agents as the drugs which can be practiced in his invention. Note col. 8, lines 27-28 and claim 15.

The substantially water-insoluble drug is dissolved in a compatible, pharmaceutically acceptable organic liquid selected from an alkane, a dialkyl ether, a long-chain ester, a hydrophobic ester, a biocompatible silicone, a biocompatible high molecular weight fluorocarbon, an oil-soluble vitamin and a volatile liquid anesthetic. See column 5, lines 9-55 and claims 2-3.

Haynes teaches using various lipids in preparing the microdroplets. Further, Haynes teaches mixtures of two or more such lipids are useful to vary the surface properties and reactivity. The lipids taught are lecithin, including the instantly claimed lecithin, cholesterol, etc (col. 5 and 6, line 56 to line 50). Lastly, Haynes teaches mixing the microdroplets with an injectable vehicle, which is an isotonic solution. See claim 5.

Hayes does not specifically teach camptothecins as the anti-cancer drug.

Burke teaches camptothecin drugs encapsulated by lipids to overcome the insolubility and instability problems of camptothecin for intravenous administration. Burke states that camptothecin drugs bind the lipid bilayer of liposomes with great affinity and intercalates between the acyl chains of the lipid. Thus, the lactone ring of the camptothecin membrane bound drug is removed from the aqueous environment *inside* and *outside* of the liposome and is protected from hydrolysis, preserving the activity of the drug. Further, Burke teaches reducing the internal pH of the liposome to prevent hydrolysis of certain camptothecin drugs. See column 3, line 59 to column 4, line 2. Burke teaches the liposomes are stable are an external pH of 7.4 and 5. See column 21, lines 1-3. Thus, the lipid encapsulation creates an internal environment

with a low pH to prevent hydrolysis of camptothecin drugs. (Note abstract). Various drug concentrations are utilized in the examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Haynes and Burke and utilize the instant camptothecin in Haynes's microdroplets. One would have been motivated to do with the expectation of similar results since firstly since Burke teaches camptothecin is a water-insoluble anti-cancer drug and Haynes clearly teaches the incorporation of any water-insoluble drugs including chemotherapeutic agents. Secondly, a skilled artisan would have reasonably expected success since Burke teaches the advantages of encapsulating water-insoluble camptothecin in phospholipid structures, which allows one to successfully deliver camptothecin by overcoming instability and insolubility problems caused by hydrolysis by the aqueous phase. Therefore, one would have expected success since Haynes's microdroplets also encapsulate the water-insoluble drug and prevent contact with the aqueous phase.

With regard to claims 6-7, a skilled artisan would have been motivated to utilize the instant pH of less than 6 for the injectable carrier since Burke teaches a low pH prevents hydrolysis of camptothecin's lactone ring, thus preserving its activity. Therefore, a skilled artisan would have been motivated to simultaneously also manipulate the pH of the injectable carrier if camptothecin is utilized as the active of choice, to preserve its activity.

With regard to claims 13-17, 25-27, it is within the skill of an artisan to manipulate the concentration of camptothecin using the guidance provided by Burke since Burke teaches several concentrations of camptothecin. Further, this is deemed to be a manipulatable parameter, which is known to those skilled in the art.

Claims 9-11 and 18-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Haynes cited above in view of Burke cited above, further in view of WO 99/61001.

As set forth above, Haynes discloses microdroplets (200 angstroms up to a micron) of water insoluble drugs containing a pharmaceutically acceptable liquid surrounded by a layer of phospholipid (Note the abstract, columns 2-8, and claims). Haynes teaches using various lipids in preparing the microdroplets. Further, Haynes teaches mixtures of two or more such lipids are useful to vary the surface properties and reactivity. The lipids taught are lecithin, including the instantly claimed lecithin, cholesterol, etc (col. 5 and 6, line 56 to line 50). Haynes teaches sterile injectable compositions. See claim 25.

As set forth above, Burke teaches claimed camptothecins encapsulated in a lipid structure and a low pH to preserve its activity.

Haynes and Burke do not teach the inclusion of tonicity modifiers (mannitol or trehalose) as claimed in independent claims 18-19 or thermally sterilizing the composition as claimed in dependent claims 10-11.

WO 99/61001 discloses suspensions of submicron and micron sized particles of water insoluble biologically active substances that are stabilized by thermoprotecting agents and that can be terminally steam sterilized without any significant increase of mean particle size. These compositions display markedly reduced heat-induced coagulation, flocculation, or particle size growth during the terminal steam sterilization process. WO teaches it is necessary to sterilize parenteral composition. However, during this process surfactants on the surface of the particle are released. The particles that are devoid of the surfactant become unstabilized and grow in size. See pages 1-2. WO's invention is directed to stabilizing particles that utilize only phospholipids

as surfactants. Specifically egg lecithin (Lipoid) is disclosed. See Table 1. Examples of suitable thermoprotecting agents include one or a combination of pharmaceutically acceptable water-soluble polyhydroxy compounds that also act as tonicity modifiers such as dextrose, sucrose, mannitol, sorbitol, and lactose. The reference teaches including these agents for protection during sterilization (note the abstract, examples and claims).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the above references and include tonicity modifiers such as trehalose or mannitol in the composition. One would have been motivated to do so since WO teaches that the instant sugars are thermoprotectants and protect the phospholipid particle suspensions during sterilization.

Response to Arguments

Applicant argues that Burke or the other cited references ignore the disadvantages of micelle structures in comparison to liposomes. Applicant argues tat Burke merely describes micelle structures as another structure for solubilizing camptothecin and does not disclose the membrane forming properties of selected lipids in relation to the amount or concentration of surface-active agents. Applicant argues that he instant microdroplets do not tend to form micelle structures and better protect the camptothecin in the presence of surfactants.

Applicant's arguments filed 6/20/05 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, the examiner points out that one not show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In

instant case, applicant's arguments are directed to Burke; however the rejection is made under Haynes in view of Burke. The examiner points out that Haynes is the primary reference that suggests the invention. Moreover, the suggestion to use a chemotherapeutic drug comes from Haynes itself. See claim 15. The only teaching lacking in Haynes is the specific disclosure of the instantly claimed anticancer drug (camptothecin). The examiner relies on the secondary reference for two reasons: 1) to teach camptothecin is a water-insoluble chemotherapeutic drug since Haynes teaches the microdroplets are suitable for any water-insoluble drug and also teaches the broad use of anti-cancer drugs and 2) the motivation to utilize the instant pH. Therefore, the fact that Burke does not teach microdroplets and teaches liposomes/micelles is moot since Haynes is not deficient in this sense. It should be noted that applicant has argued features such as the concentration of the lipids and surfactants, that are not claim limitations.

Pertinent Art

US 6,497,896 and US 6,53,080 are made of record.

Conclusion

All the claims are rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616

SSG

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